REMARKS

Claims 1-13 are pending in the present application. Claims 1-7 have been cancelled without prejudice. New claims 14-26 have been added, support for which can be found at, for example, page 4, line 26 to page 5, line 7, page 5, lines 15-24, page 6, line 14 to page 7, line 10, page 7, line 16 to page 9, line 1, and page 12, lines 14-20 of the specification. No new matter has been added. Upon entry of the present amendment, claims 8-13 and 15-26 will be pending.

The Office Action indicates that a copy of an executed Declaration filed by Applicants in response to a Notice to File Missing Parts mailed by the Office, "was not scanned into the electronic file wrapper." The Office Action requests that Applicants furnish a copy of the Declaration. As requested, Applicants attach hereto a copy of the executed Declaration.

I. The Claimed Invention Is Novel

Claims 1-2 are rejected under 35 U.S.C. §102(e) as allegedly being anticipated by U.S. Patent No. 5,489,508 (hereinafter, the "West reference"). Although Applicants do not agree, claims 1 and 2 have been cancelled without prejudice, thereby rendering the rejection moot.

II. The Claimed Invention Is Not Obvious

A. The Bischofberger Reference

Claim 3 is rejected under 35 U.S.C. §103 as allegedly being unpatentable over the combination of the West reference and U.S. Patent No. 5,633,360 (hereinafter, the "Bischofberger reference"). Although Applicants do not agree, claim 3 has been cancelled without prejudice, thereby rendering the rejection moot.

B. The Padmapriya Reference

Claim 4 is rejected under 35 U.S.C. §103 as allegedly being unpatentable over the combination of the West reference and U.S. Patent No. 5,929,226 (hereinafter, the "Padmapriya reference"). Although Applicants do not agree, claim 4 has been cancelled without prejudice, thereby rendering the rejection moot.

III. The Claimed Invention Is Not An Obvious Variant

Claims 1-4 are rejected under the doctrine of obviousness-type double patenting as allegedly being unpatentable over claims 17-21 and 23-27 of U.S. Patent 5,952,490 (hereinafter, "the Hanecak patent"). The Office Action acknowledges that the conflicting claims are not identical but nonetheless alleges that the cited claims of the Hanecak patent "are encompassed within the instantly claimed subject matter." Although Applicants do not agree, claims 1-4 have been cancelled without prejudice, thereby rendering the rejection moot.

IV. The Claimed Invention Is Clear And Definite

Claim 3 is rejected under 35 U.S.C. § 112, second paragraph, as allegedly being vague and indefinite. The Office Action alleges that "it is unclear what 'the sugar' refers to [as] there is no antecedent basis for this term." Although Applicants do not agree, claim 3 has been cancelled without prejudice, thereby rendering the rejection moot.

V. The Claimed Invention Is Enabled

Claims 1-13 are rejected under 35 U.S.C. §112, first paragraph, as allegedly "failing to comply with the enablement requirement." The Office Action asserts that one skilled in the art would have been required to perform undue experimentation to use the claimed compounds to modulate mammalian cell telomere length to treat cancer or inhibit aging. Applicants traverse the rejection and respectfully request reconsideration of the same.

Preliminarily, Applicants note that claims 1-7 have been cancelled without prejudice, rendering the rejection moot to the extent it applies to claims 1-7.

The enablement requirement of §112 is satisfied so long as a disclosure contains sufficient information that persons of ordinary skill in the art having the disclosure before them would be able to make and use the invention. *In re Wands*, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988) (the legal standard for enablement under §112 is whether one skilled in the art would be able to practice the invention without undue experimentation). In this respect, the following statement from *In re Marzocchi*, 169 U.S.P.Q. 367, 369-370 (C.C.P.A. 1971), is noteworthy:

> The only relevant concern of the Patent Office under these circumstances should be over the truth of any such assertion. The first paragraph of

> §112 requires nothing more than objective enablement. How such a teaching is set forth, either by the use of illustrative examples or by broad terminology, is of no importance.
>
> As a matter of Patent Office practice, then, a specification disclosure which contains a teaching of the manner and process of making and using the invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented ***must*** be taken as in compliance with the enabling requirements of the first paragraph of §112 unless there is reason to doubt the objective truth of the statements contained therein which must be relied upon for enabling support. (emphasis added)

The Office, save its conclusory statements, has failed to provide any sound scientific reasoning why the art-skilled could not make and use the claimed methods and compositions. Conclusory statements are insufficient to support an allegation that claims are not enabled.

The Office Action notes that claims 1-4 are included in this rejection because "the only disclosed uses for oligonucleotides which modulate mammalian cell telomere length involve therapy of cancer or inhibition of aging" and that Applicants "present no uses for a method of modulating telomere length of cells *in vitro*" (Office Action page 6). Applicants respectfully disagree. "When a product claim is not limited by a recited use, any enabled use that would reasonably correlate with the entire scope of that claim is sufficient to preclude a rejection based upon a lack of enablement." (U.S. Patent and Trademark Office Biotech Customer Partnership Meeting, April 29, 2004 presentation by Examiner Remy Yucel).

Several additional uses for the claimed oligonucleotides are set forth throughout the specification as filed. In addition to the uses noted by the Examiner (inhibiting the division of a malignant mammalian cell and modulating mammalian telomere length), other uses are set forth. For example, paragraph [0007] sets forth that "oligonucleotides which have a GGGG motif or one or more GGG motifs are useful for inhibiting viral gene expression and viral growth and for inhibiting PLA_2 enzyme activity and have long been believed to be useful as modulators of telomere length." These additional uses are described in related application 08/403,888, now U.S. Patent No. 5,952,490. Thus, the compound clearly have uses in addition to those recognized in the Office Action.

The art is not unpredictable

Applicants respectfully assert that the use of the claimed methods and compositions *in vitro* is not unpredictable. Although the Office Action alleges that "[i]n vitro, the ability of oligonucleotides to modulate telomere length is unpredictable and appears to depend on the specific cell line involved and the length of the telomeres in the cells" (Office Action, page 7), the Office Action provides no support for its allegation. Applicants direct the Examiner's attention to the several working examples specifically detailing *in vitro* methods of modulating telomere length within the present specification.

The Office Action also alleges that the art relating to the use of the claimed methods and compositions *in vivo* is not predictable, stating that "[i]n vivo, the ability of oligonucleotides to modulate telomere length so as to provide an effective therapy for treatment of cancers is untested" (Office Action, page 7). Again, the Office Action provides no support for this allegation save the conclusory statement that "more than 10 years after the effective filing date of applicants' invention, those of skill in the art are still contemplating the beginning of in vivo clinical trials ...". Applicants direct the Examiner's attention to the working example within the present specification specifically detailing *in vivo* methods of modulating telomere length in cancer cells.

Applicants also point out that the Office Action appears to be misapplying the standards for evaluating whether the enablement requirement of section 112, first paragraph have been satisfied. Applicants note that the fact that a particular method is allegedly "untested" does not render the method unpredictable. The Office Action appears to presume that Applicants' claimed methods are unpredictable even though the Office Action asserts that the methods are "untested."

As discussed above, the methods are ***not*** "untested." The methods have, in fact, been tested, results of which are set forth in the specification. Although there may be additional examples of the successful use of oligonucleotides to modulate telomere length, at the very least Applicants have successfully measured the ability of oligonucleotides to modulate telomere length both *in vivo* and *in vitro*. Applicants respectfully request that the Office Action provide logical support for its conclusion that an "untested" method is "unpredictable" and explain why the working examples of telomere length modulation provided by Applicants are not sufficient.

Applicants further point out that whether or not clinical trials have been initiated is largely irrelevant to the determination whether adequate enablement is present for the claimed invention. Indeed, the MPEP indicates that testing for safety and efficacy "is more properly left to the [FDA]." M.P.E.P. 2164.05. The MPEP further states that "considerations made by the FDA for approving clinical trials are ***different*** from those made by the PTO in determining whether a claim is enabled.") (*Id.*, citations omitted, emphasis added).

More fundamentally, the Examiner's apparent desire to see clinical data establishing efficacy of the claimed methods simply does not take into account the realities of drug development. While it might be the ultimate goal of a scientist or clinician to achieve marketing approval based upon FDA-sanctioned clinical trials, it is a reality of the business world that many attractive candidates for development cannot enter into clinical trials immediately. Delays in entering clinical trials may be due to several factors including, for example, the resources of the developing company (financial and scientific), potential market size for a product if approved, the existence of other potential medicaments with higher priorities, and the "climate" at the FDA for approving certain classes of medicaments. Indeed, any one of these factors as well as numerous others can explain the delay in entering clinical trials. However, Applicants assert that a delay in entering a clinical trial is ***not*** evidence of unpredictability.

The references cited by the Office Action that are alleged to discuss the delays in entering clinical trials do not support the Office Action's allegation that the art is unpredictable. Indeed, Applicants note the large number of groups pursuing clinical application of telomere length modulation as proof that the art skilled believe in the predictability and practicality of telomere modulation as a therapeutic. The references also discuss numerous *in vitro* and *in vivo* assays of telomere length modulation. Further, Applicants note that the references point out the attractiveness of antisense mediated telomere length modulation. For example, Helder et al. (Cancer Investigation, 2002, 20, 82-101; hereinafter "the Helder reference") at page 90 states that "inhibition with some kinds of AS ONs might provide a less complicated, but comparably effective alternative [to the use of hTR-expressing vectors]". The Helder reference also notes successful *in vitro* and *in vivo* use of antisense oligonucleotides (see page 95).

Notably, the references cited in the Office Action actually provide a logical explanation for the delay of *in vivo* clinical trials. Rezler et al. (Ann. Review of Pharmacology and Toxicology, 2003, 45, 359-79; hereinafter "the Rezler reference") discusses why such delays are seen in clinical trials. Specifically, the Rezler reference states that:

> Most solid tumors have population doubling times of several days to several weeks, suggesting that anti-telomerase therapies could take months to produce any effect in a patients cancer. These difficulties have slowed the development of telomerase inhibitors in the clinic.

(see page 362). Notwithstanding, however, the Rezler reference further states that "the telomere/telomerase research area is moving toward clinical trials of the best chemical agents." (see page 374). Taken as a whole, the references cited in the Office Action do not support the contention that the art is unpredictable. The references discuss results of *in vivo* and *in vitro* assays and provide reasons for delays in entering clinical trials.

The Office Action further alleges that issues exist regarding the delivery of oligonucleotides, reproducibility of date, and the lack of correlation between animal data and human efficacy. The Office Action cites Nature Biotechnology, 1997, 15, 519-524 (hereinafter the "Nature Biotechnology reference") and Branch (TIBS, 1998, 23, 45-50; hereinafter, the "Branch reference") in support of its allegation. Applicants do not agree with the conclusions drawn from these references. Indeed, the references cited by the Office Action, do not support the allegation that the delivery of oligonucleotides is problematic, that data is unpredictable, and that there is no correlation between *in vitro* and *in vivo* results.

Although the Office Action cites the Branch reference as supporting its allegation of unpredictability, the Office Action has failed to cite any particular portion of the Branch reference that supports its assertion that oligonucleotide technology is unpredictable. Nonetheless, the Branch reference does not teach that oligonucleotide technology is unpredictable or that any technical difficulties discussed are insurmountable. Rather, the Branch reference concludes by saying, among other statements, that "there is growing evidence that antisense molecules can be useful pharmacological tools when applied carefully," (Branch, page 50), indicating that the skilled artisan sees promise in the use of oligonucleotide technology and,

although some experimentation may be required to refine the parameters, this experimentation would not be undue.

The Nature Biotechnology reference discusses the state of the biotech industry "as antisense drugs advance through clinical trials." Although the Nature Biotechnology reference discusses issues involved with the use of antisense drugs, the reference fails to provide any evidence that one skilled in the art would not be able to make and use the claimed invention. In fact, the Nature Biotechnology reference taken as a whole discusses the advances in the field that had overcome several of the issues noted and painted an optimistic picture for the antisense industry. For example, James Wyngaarden indicates that "[o]ne by one, they [antisense companies] are getting around what had initially seemed to bee very important problems. It seems that shortly they will no longer be so important" (Nature Biotechnology, page 519). Arthur Levin discusses *in vivo* data relating to the BCL2 gene, stating that the data "is a brilliant example of specificity" (Nature Biotechnology, page 521). Benjamin Weiss also commented on *in vivo* data, noting that "a great deal of specificity has been demonstrated in some in vivo studies using antisense oligonucleotides" (Nature Biotechnology, page 521). Several attendees discussed the alleged lack of reproducibility. "Conference Attendee 2" stated that "the lack of reproducibility has to do with the optimization of conditions... I think if those conditions are adhered to, lots of reports are reproducible" (Nature Biotechnology, pages 522-3). "Conference Attendee 3" stated that "there is a lot of good correlation between in vitro behavior and in vivo pharmacokinetics and activity" (Nature Biotechnology, page 523). Arthur Krieg attributed the perceived lack of reproducibility to unpure oligonucleotides from suppliers, noting that "this can also affect the reproducibility of results" (Nature Biotechnology, 523). Arthur Levin summarized the increased scrutiny placed on antisense compounds, stating that "you are putting these compounds [antisense compounds] under a microscope that no other class of compounds is required to be under ... So I am worried that you are asking more of these compounds than you would of other drugs" (Nature Biotechnology, page 524). Finally, Stanley Crooke encourages "people to look at this period as the end of the beginning of antisense" (Nature Biotechnology, page 524). Clearly, many of the comments in Nature Biotechnology do not support the position that use of oligonucleotides *in vivo* is unpredictable, that the data is not reproducible, or that

there is a lack of correlation between animal data and human efficacy.

The Office Action also alleges that the cited references demonstrate that undue experimentation would be required to make and use the present invention *in vivo*. However, just because some experimentation may be required does not make it undue. "The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." (M.P.E.P. § 2164.06). The present application provides a ***reasonable amount*** of guidance with respect to the direction in which the experimentation should proceed. The present specification outlines the types of compounds that can be used and methods used to modulate telomere length. The experiments that a person of ordinary skill in the art may have to undertake to use the invention do not make it undue. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." (M.P.E.P. § 2164.01). The types of experiments that the Office Action alleges are merely routine in the art, even if they are complex.

The Office Action also alleges that there is no correlation between *in vitro* and *in vivo* results. However, absolute certainty is not required. Instead correlation is dependent on the overall state of the prior art. The M.P.E.P sets forth that it is the overall the state of the art that is important for determining the unpredictability of a field, not one or two references. The M.P.E.P states:

> In this regard, the issue of 'correlation' is also dependent on the state of the prior art. In other words, if the art is such that a particular model is recognized as correlating to a specific condition, then it should be accepted as correlating unless the examiner has evidence that the model does not correlate. Even with such evidence, ***the examiner must weigh the evidence for and against correlation and decide whether one skilled in the art would accept the model as reasonably correlating to the condition.*** In *re Brana,* 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995) (reversing the PTO decision based on finding that *in vitro* data did not support *in vivo* applications)...***A rigorous or an invariable exact correlation is not required*** as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224, USPQ 739, 747 (Fed. Cir. 1985).

(M.P.E.P 2164.02, emphasis added). It appears that the Office Action is under the impression

that an "exact correlation" is required, while the M.P.E.P clearly states that it is not. Enablement does not require 100% success. In *Wands*, the claims were found to be enabling even though only 4 out of 143 (only 2.8%) hybridomas producing monoclonal antibodies were successful. *In re Wands*, 8 U.S.P.Q.2d 1400, 1406 (Fed. Cir. 1988).

Contrary to the Office Action's allegations, there has been a great deal of success and correlation between *in vitro* and *in vivo* results in the field of antisense. A recent survey of the scientific literature demonstrates that there is a correlation between *in vitro* results and *in vivo* data in the state of the art of the present invention and that it is not unpredictable. This survey demonstrates numerous examples of correlation between *in vitro* experiments and *in vivo* experiments. For example, in Smith et al. (Clinical Cancer Research, 2001, 7, 400-406), data is discussed demonstrating inhibition of bcl-2 expression in vitro and in vivo. In O'Dwyer et al. (Clinical Cancer Research, 1999, 5, 3977-3982), results are discussed where the administration of an antisense compound inhibited the expression of c-raf-1 mRNA *in vitro* and *in vivo*. Based on these results the authors performed a clinical trial in human patients where they also saw expression of c-raf-1 inhibited. In Miyake et al., (Clinical Cancer Research, 2000, 6, 1655-1663) the authors provide data that show the inhibition of TRPM-2 both in vitro and in vivo. In Berg et al., (The Journal of Pharmacology and Experimental Therapeutics, 2001, 298, 477-484) the authors demonstrate *in vitro* and *in vivo* inhibition of the expression of thymidylate synthase. In Tortora et al., (Clinical Cancer Research, 2001, 7, 2537-2544) the authors discuss in the introduction previous results of where antisense oligonucleotide against protein kinase alpha type I (PKAI) inhibit expression *in vitro* and show antitumor activity *in vivo*. In Tortora the authors combine PKAI antisense compounds with bcl-2 antisense compounds and demonstrate *in vitro* inhibition along with anti-tumor activity *in vivo* characterized by reduced tumor volume and an increase survival, which is assumed to be due to the inhibition of PKAI and bcl-2. *Id.* Applicants attach hereto copies of the above-identified references that demonstrate a correlation between *in vitro* and *in vivo* data. These articles and others available in the art demonstrate that a person of ordinary skill in the art would accept that *in vitro* data ***does*** correlate with *in vivo* data.

When taken as a whole the state of the art, including the references cited by the Office Action, do not support the allegation that the delivery of oligonucleotides is problematic, that

data is unpredictable, and that there is no correlation between *in vitro* and *in vivo* results. Therefore, the field of antisense is not unpredictable. A person of ordinary skill in the art would not believe the Office Action's assertion that there is no correlation between *in vitro* data and *in vivo* data.

The Office Action alleges that "no examples of the claimed invention" are provided. Paradoxically, however, in the very next paragraph, the Office Action discusses Applicants' examples "whereby telomere length in immortalized cell lines and human xenografts in nude mice was reduced after administration of the instantly recited oligonucleotides." (Office Action, page 8). Applicants respectfully direct the Examiner's attention to the present specification which sets forth several examples that teach how to use the claimed invention. Example 2 describes the *in vitro* modulation of telomere length in fibroblasts. Example 6 describes how to deliver oligonucleotides to the targeted cells. Example 7 teaches the modulation of telomere length *in vitro* in HME-50 cells (human primary breast epithelial cell line) and in DU145 cells (human prostate cancer cell line). Example 8 teaches the modulation of telomere length *in vivo*.

The Office Action again questions the relevance of Applicants' *in vitro* and animal model data to the *in vivo* efficacy for treatment for cancer or aging based on the lack of clinical trials. Applicants again point out that the MPEP clearly sets forth that exact correlation between data is ***not*** required. The discussion of correlation of data discussed above is incorporated herein by reference.

The Office Action concludes that although the level of skill in the oligonucleotide and telomere art is high, "given the broad scope of the claims, the lack of guidance in practicing the claimed invention, the poorly developed state of the art and the high level of unpredictability in the art, it must be considered that the skilled artisan would have needed to have conducted essentially trial and error experimentation in order to practice the claimed invention." (Office Action, page 9). Applicants do not agree.

As discussed above, Applicants provide detailed guidance on how to practice the invention, including working examples of *in vivo* and *in vitro* modulation of telomere length. The art is not unpredictable. The fact that clinical trials have not yet commence does not mean

that the methods are unpredictable. Indeed, the data provided by Applicants provides predictability to the claimed methods.

If the Office Action maintains the enablement rejection with only written allegations that appear to be based solely on the knowledge of the Examiner, Applicants respectfully request that the Examiner submit an affidavit as to why the present application is not enabled in view of the absence of other scientific evidence (*i.e.* scientific publications).

The art-skilled would readily be able to make and use the compounds within the scope of the pending method and composition claims. Applicants have provided at least one method for making the claimed invention that "bears a reasonable correlation to the entire scope of the claim". The Office Action has failed to provide any "adequate reasons" as to why a person skilled in the art could make and use the claimed invention without undue experimentation. Thus, the Office Action has failed to establish a *prima facie* case of nonenablement. Accordingly, Applicants respectfully request withdrawal of the rejection under 35 U.S.C. 112, first paragraph.

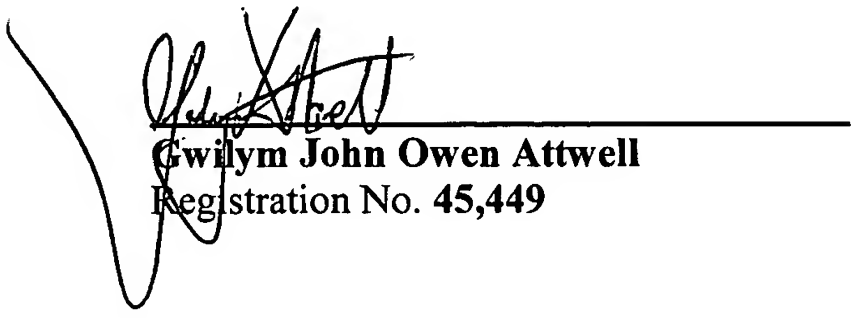
One having ordinary skill in the art would be able to make and use the claimed invention using the application as a guide. Applicants cite numerous references that support enablement. Based on the evidence as a whole, the claims are enabled -- one of ordinary skill in the art would be able to make and use the claimed invention without undue experimentation using the application as a guide. The field of antisense is not unpredictable. In addition, one skilled in the art would believe that *in vitro* data correlates with *in vivo* data. No undue experimentation is required to practice the pending claims. Thus, the pending claims of the present application are enabled. Accordingly, Applicants respectfully request that the rejection of claims 8-13 under 35 U.S.C. § 112, first paragraph be withdrawn.

Because enabled uses exist for the oligonucleotides of the present invention, Applicants respectfully request the withdrawal of the 35 U.S.C.§ 112, first paragraph, at least with respect to the oligonucleotide claims.

VI. Conclusion

In view of the foregoing, Applicants respectfully submit that the claims are in condition for allowance. An early notice of the same is earnestly solicited. The Examiner is invited to contact Applicants' undersigned representative at (215) 665-6904 if there are any questions regarding Applicants' claimed invention.

Respectfully submitted,



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Enclosures
-copy of executed Declaration
-Smith et al. (Clinical Cancer Research, 2001, 7, 400-406)
-O'Dwyer et al. (Clinical Cancer Research, 1999, 5, 3977-3982)
-Miyake et al., (Clinical Cancer Research, 2000, 6, 1655-1663)
-Berg et al., (The Journal of Pharmacology and Experimental Therapeutics, 2001, 298, 477-484)
-Tortora et al., (Clinical Cancer Research, 2001, 7, 2537-2544)